CLINICAL PROCEEDINGS

of the

CHILDREN'S HOSPITAL

WASHINGTON, D. C.

April 1953

VOLUME IX NUMBER 4

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OF THE CHILDRENS HOSPITAL

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THE ELECTROCARDIOGRAM IN ELECTROLYTE IMBALANCE

Special Report No. 260

John O. Nestor, M.D.

The electrocardiogram has become increasingly important in the detection of disturbances of electrolyte balance since it has become more apparent that abnormalities in the concentration of the main cations (potassium, sodium, calcium, magnesium) in the extracellular fluid and the circulating blood are reflected in electrocardiogram changes and can be recognized as such to a certain degree.

It must be understood that a significant change in concentration of one of these ions will result in changes in the concentration of the other ions and thus the electrocardiogram records the total effect. For instance, an increase in the concentration of sodium antagonizes, while a decrease enhances the characteristic effect of potassium on the electrocardiogram The effect upon the electrocardiogram of variations in the concentration of other ions such as calcium and magnesium has not been fully worked out or clearly demonstrated as yet.

Little is known, except by inference, about the effect on the electrocardiogram of variations in intracellular electrolyte composition but we know a great deal more about the effect of changes in extracellular electrolytes upon the electrocardiogram. Since the electrolyte balance of the interstitial and intracellular fluid is usually altered before that of the serum it would seem that the electrocardiogram would be a more sensitive index of the total electrolyte picture than the serum levels of the substances involved. The electrocardiogram will not only indicate that there is a significant electrolyte imbalance but also whether the change is in the direction of hypokalemia or hyperkalemia since the changes due to abnormalities of potassium concentration are more marked and characteristic than those due to changes in the concentration of the other cations present. Because of this we are listing below the causes of change in potassium concentration, the main signs and symptoms resulting there from, the concomitant changes in the electrocardiogram, and the treatment indicated.

HYPERKALEMIA (HYPERPOTASSEMIA)

Clinical Conditions Causing Hyperkalemia:

1. Renal insufficiency
2. Untreated diabetic acidosis
3. Excessive ingestion of potassium
4. Adrenal cortical insufficiency

Signs and Symptoms:

1. Listlessness and mental confusion
2. Numbness, tingling, and weakness of the extremities
3. Pallor
4. Bradycardia and irregular rhythms
5. Peripheral vascular collapse
6. Ascending flaccid paralysis
7. Cardiac arrest

Electrocardiographic Changes:

1. High peaked T waves
2. Low R waves
3. Prolonged PR interval*
4. Absence of P waves
5. Prolonged QRS interval
6. Depressed ST segments*
7. Biphasic QRS and T waves
8. Total arrythmia
9. Cardiac arrest*

Treatment:

1. Intravenous saline, glucose, and insulin
2. Dialyses with artificial kidney
3. Peritoneal lavage
4. Desoxycorticosterone

HYPOKALEMIA (HYPOPOTASSEMIA)

Clinical Conditions Causing Hypokalemia:

1. Therapy of diabetic acidosis
2. Intestinal obstruction (loss of gastro-intestinal secretions)
3. Desoxycorticosterone intoxication
4. Familial periodic paralysis
5. Therapy of diarrhea
6. Therapy of adrenal cortical insufficiency (ACTH and cortisone)
7. Renal disease
8. Inadequate potassium intake
9. Excessive parenteral fluids
10. Alkalosis

Signs and Symptoms:

1. Weakness and hypotonia of skeletal muscles progressing to frank paralysis

* These findings are common to both conditions.

2. Dyspnea and gasping
3. Cyanosis
4. Abdominal distension
5. Nausea and vomiting
6. Cardiac enlargement and systolic murmurs
7. Increased pulse pressure
8. Elevated venous pressure
9. Cardiac failure and arrest

Electrocardiographic Changes:

1. Low voltage
2. Prolonged QT interval
3. Low, rounded, and prolonged T waves
4. Inversion of T waves
5. Depressed ST segments*
6. Prolonged PR interval*
7. Possible inversion of P waves
8. Prominent U waves
9. Extrasystoles and AV block
10. Cardiac arrest*

Treatment:

Potassium solutions

SUMMARY

The role of the electrocardiogram in detecting electrolyte imbalance has been discussed with the emphasis on the causes, clinical picture, electrocardiographic changes and the treatment of abnormalities of potassium metabolism since variations in the concentration of potassium in the extracellular fluid and circulating blood produce the most marked and characteristic effects of all the cations present.

PRIMARY MALIGNANT TUMOR SIMULATING A SOLITARY PULMONARY METASTASIS

Case Report No. 261

Marshall C. Sanford, M.D.
John E. Cassidy, M.D.

Primary tumors of the lung are extremely rare during infancy and childhood. Pulmonary metastases from tumors arising elsewhere, however, commonly occur, but usually they are multiple and widespread represent-

ing the terminal stages of the disease. Wilms' tumor, the most frequently encountered neoplasm during infancy, tends to spread by way of the blood stream to the lungs. We know of only one case in which a solitary pulmonary metastasis of such a tumor was successfully resected. In adults the reported incidence of successful removal of a solitary pulmonary metastasis, especially from gastrointestinal neoplasms, is increasing. The case herein reported appeared at first to be a Wilms' tumor of the right kidney with a solitary metastasis to the lung. The final diagnosis, however, proved this assumption to be incorrect, and the problems of diagnosis and management are presented.

Case Report C. F. 51-14776

This three-year-old white boy was admitted to Children's Hospital on December 12, 1951 complaining of pain in the left chest of three days' duration. He had been healthy all of his life but his mother thought that he had been somewhat anorexic during the preceding six weeks. Three days prior to admission, he began to complain of dull, aching pain in the left upper chest. He had no cough nor evidence of upper respiratory infection. His temperature was 101°F., but he did not appear ill. Examination of the chest revealed dullness to percussion over the left upper chest both anteriorly and posteriorly with absence of breath sounds in these areas. There was a mass palpable in the right upper quadrant of the abdomen which felt smooth, rounded, and fixed. Roentgenogram of the chest revealed an opacity throughout the left lung with the suggestion of a mass in the left upper lobe.

A thoracentesis was productive of a moderate amount of thin, blood-tinged fluid which on pathological examination failed to reveal abnormal cells. On repeat x-ray examination of the chest after thoracentesis, a grape-fruit sized, solitary mass in the left upper chest was clearly visualized.

A flat plate of the abdomen and intravenous pyelogram revealed the left kidney to be normal but the right kidney was displaced laterally with compression and distortion of the pelvis and calyces. The diagnosis of a Wilms' tumor of the right kidney with a solitary pulmonary metastasis to the left upper lobe was made. We realized our hope for a cure was remote if our provisional diagnoses were correct and our only chance to attain this cure had to include extirpation of these masses. We elected to attack the abdominal mass first since we considered it the primary site, and, unless we found obvious metastases, to follow this with thoracotomy and resection of the pulmonary tumor.

On December 18, 1951 the patient was taken to the operating room where a laparotomy was performed. The left kidney was normal to palpation; the liver and abdominal lymph nodes appeared uninvolved. A soft, cystic, multiloculated mass about the size of one's fist involved the right kidney. The entire tumor mass and kidney were resected. Grossly, the mass appeared to be a Wilms' tumor, but on pathological examination, it was found to be a benign multicystic kidney.

On December 19, 1951, the day following nephrectomy, a left thoracotomy was performed under cyclopropane and ether anesthesia. A grape-fruit sized, solid tumor mass filled most of the left chest and compressed the lower lobe. The tumor was smooth and was completely covered by compressed but otherwise normal pulmonary tissue. The mediastinal lymph nodes were not enlarged. A small amount of blood-tinged fluid was present in the pulmonary cavity. Grossly the tumor appeared be-

nign and a left upper lobectomy was performed. The lower lobe expanded nicely once the compressing tumor was removed. During the closure of the chest wall, the anesthetist announced that the heart had suddenly stopped; the chest was reopened at

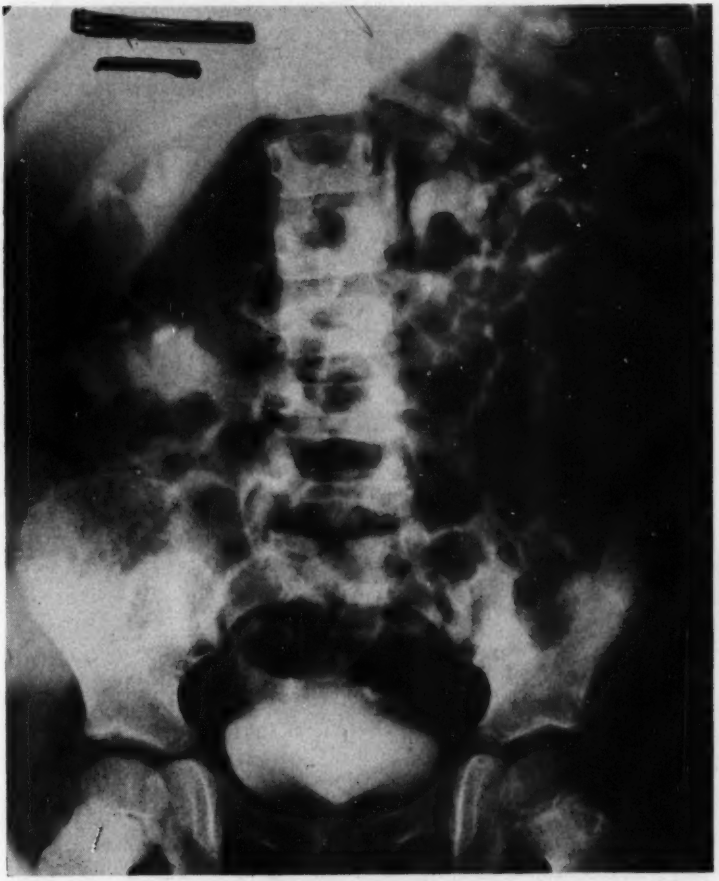

FIG. 1. Intravenous pyelogram. Note mass in right upper quadrant which distorts the renal pelvis and calyces.

once and the heart was found to be cyanotic and not beating. Cardiac massage was immediately instituted and, without the aid of stimulants, normal rhythm was resumed. After several minutes' observation during which the heart rate and rhythm appeared normal, the chest was closed and the patient was returned to the ward in good condition.

Pathological report of the resected pulmonary tumor revealed it to be a malignant teratoma. Undifferentiated cells with frequent mitoses could be seen; embryonal cartilage, fibrous tissue, and areas of necrosis and hemorrhage were scattered throughout. There was no clear-cut delineation between the tumor from the adjacent pulmonary tissue which was compressed. X-ray therapy over the left chest and mediastinal areas was initiated and was continued for two courses following discharge. On January 1, 1952, fourteen days after admission, the patient was discharged from the hospital—afebrile and asymptomatic.

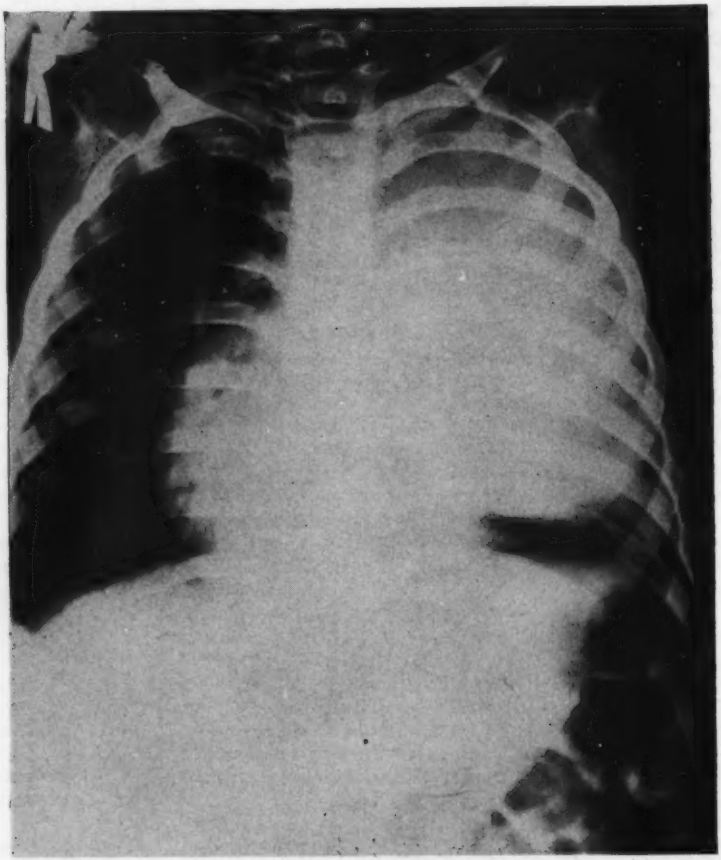

FIG. 2. Preoperative x-ray of the chest. The giant-sized tumor almost fills the entire left chest. Note mediastinal shift to right.

At home he gained weight; his appetite was good, and he was able to resume normal

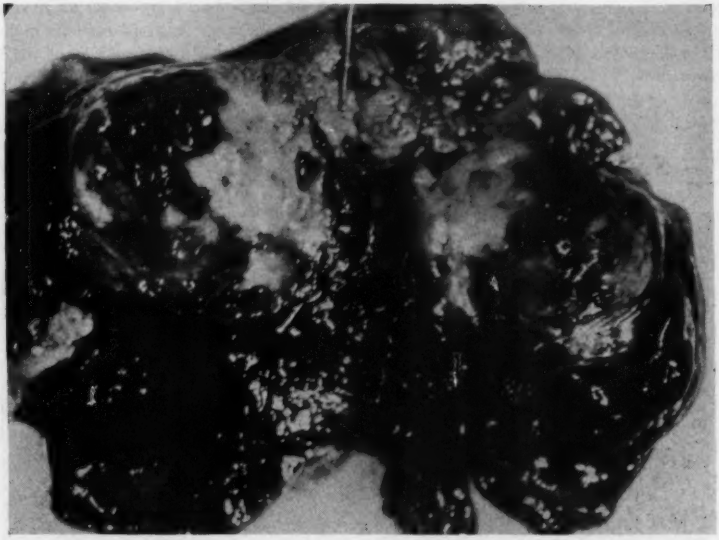

FIG. 3. Left upper lobe and giant pulmonary tumor. Note rim of compressed lung which surrounds the tumor.

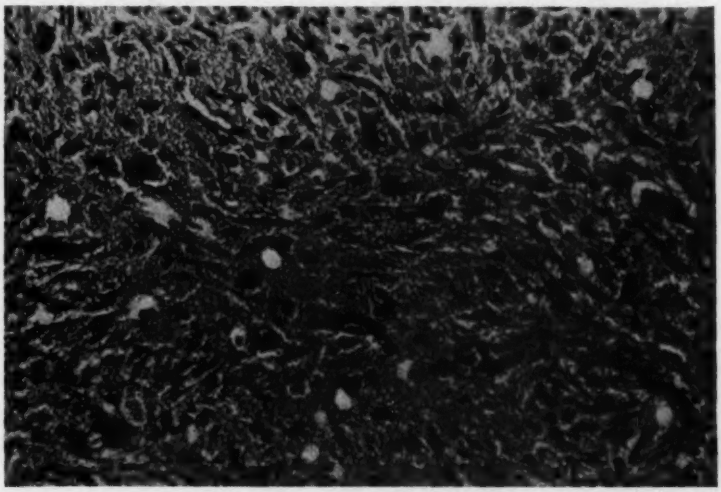

FIG. 4. Photomicrograph of pulmonary tumor shows fibrous tissue and cartilage with areas of hemorrhage and necrosis.

physical activity. Follow-up roentgenograms of the chest were made at monthly intervals and failed to reveal any evidence of pulmonary metastasis until six months after operation when a small solitary shadow appeared in the midportion of the left lower lobe. This was observed for two weeks, during which time it became somewhat more conspicuous, however, there was no other evidence of spread. This shadow was thought to represent a solitary metastasis—probably a local extension of the original tumor. It became apparent that his prognosis was grave, but it was hoped that an extrapleural removal of the remaining lung and pleura might eradicate the tumor.

On June 19, 1952 an extrapleural left lower lobectomy and pleurectomy were performed. Unfortunately, examination of the resected specimen revealed the presence

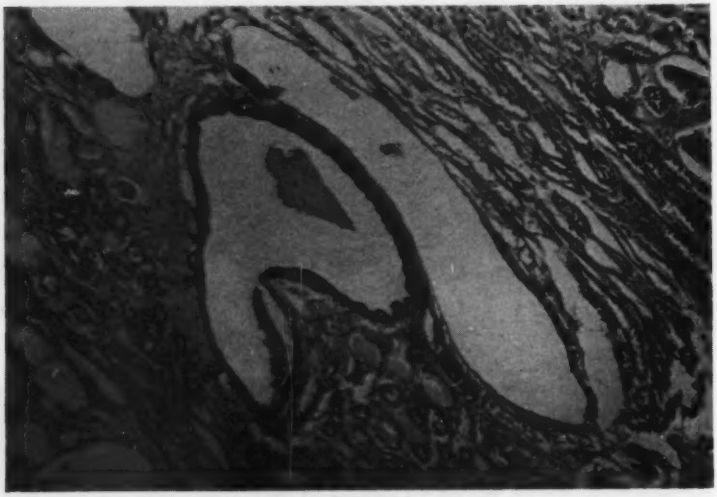

Fig. 5. Photomicrograph of cystic kidney. Low cuboidal epithelium lines the wall of the cysts.

of many small metastases in addition to the one already visualized on x-ray. Thereafter the patient's course was rapidly downhill. Although he was allowed to go home soon after operation he returned to the hospital within a month complaining of pain in the back, left thigh, and right shoulder. He had developed an empyema on the left and x-rays revealed destructive lesions of the thoracic vertebrae, scapula, and femur which, undoubtedly, were due to metastases. The empyema was drained under local anesthesia, but the patient's condition continued to deteriorate; respiratory distress became severe, and he expired on July 12, 1952.

Autopsy revealed a large retroperitoneal mass which extended from the tail of the pancreas into the posterior mediastinum. The left adrenal gland was invaded by the neoplasm. The right pleural surfaces contained a few, small tumor nodules which pressed into the pulmonary tissue but there appeared to be no spread throughout the lung parenchyma.

The opinions of the pathologists varied as to the exact histological nature of the tumor. Some maintained that it was a malignant teratoma which originated in the

left lung and metastasized, while others considered it to be a fibrosarcoma which arose in the retroperitoneal space and extended locally as well as systemically. All concurred that the renal lesion was a benign, multicystic kidney.

DISCUSSION

This three-year-old white boy died approximately eight months following resection of a large pulmonary tumor which later metastasized throughout the body. This case is presented to illustrate some of the procedures which seem indicated in the management of malignancy in childhood and to combat the defeatist attitude toward this entity if any therapeutic triumphs are to be achieved.

Before the initial operation some physicians reasoned that no surgical intervention was justified on the basis that we were dealing with a malignant Wilms' tumor of the kidney which already had metastasized to the lung. When operation revealed the renal lesion to be benign, however, they agreed that thoracotomy was indicated to determine the nature of the pulmonary mass. How pathetic would have been the situation had we refused treatment only to find later that both lesions were benign. Such was not the case with this child, and the pulmonary lesion was highly malignant and later was responsible for the patient's death. The opposite situation might have existed in which a resectable malignant kidney lesion precluded the excision of a benign pulmonary tumor. For these reasons, we feel that the only course open to physicians striving to cure cancer in children is to take aggressive action and to make every effort within reason to eradicate the disease. Only after these measures have been exhausted do palliative forms of therapy find their place.

FAMILIAL AUTONOMIC DYSFUNCTION; ITS OCCURRENCE IN TWO SIBLINGS

Case Report No. 262

David A. St. Martin, M.D.

INTRODUCTION

Recently a new clinical entity known as familial autonomic dysfunction has been described by Riley[1]. In view of the absence of any definitive pathologic or anatomic changes, the nomenclature of the disease was predicated on the fact that it tends to run in families and involves primarily the autonomic nervous system. The following case reports are illustrative of the clinical manifestations encountered in this disease entity together

with an indication of its genetic origin. These two cases represent the first instances of this disease encountered in the Washington area.

CASE REPORTS

Case No. 1. L. F. 51-4753

L. F., a white female born November 15, 1950 of Jewish descent, has had five hospitalizations, three of which were at Children's Hospital at ages 5, 6, and 12 months of age. In each instance the chief complaint was that of fever of undetermined origin.

Family history revealed the patient's father to be 52 years of age and in good health. There were 9 children by a previous marriage. One of these children died at 3 months of age of unknown cause, but the remaining 8 had been apparently normal. In 1944 all of the children as well as their mother were exterminated in a German concentration camp. The father married again in 1945. The first child of this marriage died at 17 months of age in Germany. This child had had a poor weight gain and had been hospitalized several times for respiratory infections. Bilateral corneal ulcers were reported to have developed when the child was 15 months old. L. F. was the second child of this marriage and her younger sibling, D. F., the next case to be presented, was the third progeny. The latter two children were born in Washington, D. C. after the parents had immigrated to this country.

The mother, age 32, was in good health. No familial diseases were known to exist in the families of either parent except possibly for asthma in the maternal grandfather.

Past history showed the prenatal, natal, and postnatal periods to have been normal. The birth weight was 6 pounds, 14 ounces. She was breast fed for three weeks and then placed on an evaporated milk formula with vitamin supplements. She vomited a portion of each feeding from birth until approximately 5 months of age. At 9 months the patient could hold her head erect, but she was unable to sit unaided at 12 months.

Since the age of 5 months, the patient has had remittent temperature elevations ranging between 104.0 F. to 106.0 F. of seven to ten days' duration followed by remissions lasting one to two weeks. Characteristically, the temperature became elevated in the morning with some defervescence in the afternoon. Accompanying the return of the temperature to normal, there was profuse perspiration. Severe vomiting episodes paralleled the fever. During the afebrile periods, the patient was apparently well.

Physical examination revealed a poorly-developed white female who was irritable and febrile. Blotching of the skin as well as profuse sweating were observed during the course of the examination. The temperature was 102.0 F., pulse 110, and respirations 32 per minute. A non-infected sinus was present over the sacrum. No tears were noted at any time even with vigorous crying. On the last of three admissions, a right corneal ulcer was noted. The remainder of the physical examination was not remarkable except for tardy motor development.

Laboratory examinations included blood, urine, stool, and cerebrospinal fluid cultures, complete blood counts, bone marrow examination, urinalyses, malarial smear, eosinophil counts, eosinophil tolerance test, erythrocyte sedimentation rate, blood chemistries, febrile agglutinations, heterophile agglutination, tuberculin and histoplasmin skin tests, chest, skull, and long bone roentgenograms, intravenous and retrograde pyelograms, pneumoencephalogram, electroencephalogram, skin and

muscle biopsy, skin resistance tests, and subdural and lumbar punctures. Except for the following, the above examinations were ostensibly negative or normal: repeated blood counts revealed a mild leukocytosis (15,000) with 65 to 90 per cent lymphocytes; proteus vulgaris and pseudomonas aeruginosa were obtained from urine culture on three separate occasions, and on the first admission a roentgenogram of the chest revealed a bilateral pneumonia.

Substantiating the history, the patient's temperature showed an early morning rise reaching 106.0 F. on occasions. These daily spikes of temperature occurred throughout the period of each hospitalization. Profuse perspiration, especially on crying or while feeding, was noted. When proteus vulgaris was cultured from the urine, the patient was placed on chloramphenicol without response. The fever was controlled to some extent with aspirin and alcohol sponging.

During the second admission, the patient was again given antibiotic drugs with equivocal results. Cortisone (25 milligrams per day) was given on the third admission along with antimicrobial agents. A discharge diagnosis of familial autonomic dysfunction was entertained following exclusion of most other causes of cryptogenic fever.

The patient is now 28 months of age, has continued to run intermittent fevers and has failed to do well. Profuse perspiration, blotching of the skin, motor retardation, and slow physical development are still in evidence. The corneal ulcer in the right eye remains unchanged and defective lacrimation has continued.

Case No. 2 D. F. 52-8521

D. F., a white female born on July 12, 1952, is the sibling of the patient presented above. This little girl has had three hospitalizations at 6, 7 and 20 weeks of age for fever and dehydration.

The past history revealed the prenatal, natal, and postnatal periods to be normal. The birth weight was 7 pounds, 13 ounces. A few days after birth, a mild diarrhea developed and it was controlled by a high protein milk. Another bout of diarrhea was observed when orange juice was initiated.

The patient began having morning temperature elevations at approximately 5 weeks of age and as with her older sister, the temperature dropped in the afternoon. Vomiting accompanied these febrile episodes. Profuse perspiration was a prominent feature in this patient's history also. These febrile episodes were separated by periods of normal temperature ranging from one to four weeks.

Physical examination revealed a moderately well-developed 6-week-old white girl who was very irritable and perspired profusely. The temperature varied between 102.0 F. and 105.0 F. on each of three admissions. Mild dehydration was manifest. Defective lacrimation was observed but no corneal ulceration was in evidence. Dyspnea, tachypnea, and rhonchi were noted during the second admission accompanied by a soft liver edge which was palpable 3 centimeters below the right costal margin in the mid-clavicular line. No splenic enlargement was apparent. The remaining portion of the examination was substantially negative.

Laboratory examinations performed during the three separate admissions included: urinalyses, complete blood counts, blood and stool cultures, eosinophil counts, eosinophil tolerance test, cerebrospinal fluid, tuberculin skin test, chest roentgenograms and carbon-dioxide combining power. Except for a variable leukocytosis (13,000 to 20,000) with a normal differential and an x-ray showing bronchopneumonia on the second admission, the various tests were negative or normal.

Within a short period after each admission the patient's temperature returned to normal. There was a brief period of dyspnea during the first admission which responded to oxygen therapy and did not recur until the time of the second hospitalization. Penicillin was used for treatment of a respiratory infection present at the time of the second admission. When opisthotonus was observed, lumbar and subdural punctures were performed, both with negative results. Parenteral fluids were necesary during the second admission as well as during the last admission when dehydration was apparent.

Following discharge in November 1952, the patient has continued to run intermittent high fevers of cryptogenic origin with concomitant vomiting and marked hyperhidrosis. She has followed almost the identical clinical pattern of her older sibling except for the absence of corneal ulcerations.

DISCUSSION

Sidney Ross, M.D.. Both of these children presented a rather difficult diagnostic problem although after the diagnosis was made in the older sibling (L. F.), it became quite apparent in the younger child. The presenting symptoms of intermittent fever of prolonged duration, excessive prespiration, defective lacrimation, skin blotching, periodic vomiting and corneal ulceration together with the fact that these children are of Jewish extraction made the diagnosis of familial autonomic dysfunction a relative certainty. As was indicated, an extensive laboratory workup on both children revealed no other cause for these clinical manifestations. Riley recently reported a series of 33 cases of familial autonomic dysfunction in which a definitive picture of this syndrome was clearly demonstrated. All 33 cases had many features in common justifying the concept that they were examples of a real and easily recognizable clinical entity of familial nature. This syndrome was characterized primarily by disturbances in function of the autonomic nervous system. In Riley's series the cardinal features occurring in almost 100 per cent of the cases included defective lacrimation, skin blotching, excessive perspiration, drooling, emotional instability, motor incoordination and hyporeflexia. Other manifestations of vegetative dysfunction occurring in 35 to 85 per cent of cases included hypertension, cyclic vomiting, frequent unexplained fever, mental retardation, convulsions, and corneal ulceration. All 33 patients in Riley's series were of Jewish extraction.

Of singular interest is the familial incidence of this disease. Of a total of 33 cases in Riley's series, 11 siblings were known to be affected. Riley suggested this proportion was compatible with a Mendelian recessive characteristic. As for the genetic consideration in our cases, both siblings have followed an identical course and a third sibling who died in Germany at the age of 15 months had a corneal ulceration at the time of his death On close questioning of the parents, it was apparent that this child also had periodic episodes of unexplained fever, excessive perspiration, defective lacrimation

and frequent episodes of pulmonary infection. There appears to be little doubt that this child similarly had familial autonomic dysfunction. The genetic aspects are rather striking in that the father had 9 children by his previous marriage, 8 of whom survived and were living and well until their untimely death in a concentration camp. Prior to their extermination, these children had displayed no evidence of familial autonomic dysfunction. However, all three progeny resulting from the second marriage have been afflicted with the disease. It would appear that the second wife carried the Mendelian characteristic and would suggest that it is probably a dominant rather than a recessive characteristic in this instance.

In Riley's series, 9 cases came to autopsy. However, no definitive pathologic finding was observed in the central nervous system of any of these cases who died.

In regard to treatment, it has been primarily symptomatic in an attempt to modify the more disturbing manifestations of the disease such as vomiting, hypertension, defective lacrimation, and the extreme emotional instability. Riley describes the use of various types of anticonvulsants and sedatives, autonomic-active drugs, muscle relaxants and cortisone. However, none of these modalities of therapy appeared to produce any significant improvement. One of our cases received cortisone and ACTH and similarly appeared to derive no particular benefit. As for surgical procedures, Riley has reported on the use of lumbo-sympathectomy and splitting of the tentorium in a small number of cases. However, no lasting benefit was produced. In one of Riley's cases, a prefrontal lobotomy was performed and produced a cessation of pernicious vomiting for one month after the procedure was done. However, a relapse appeared shortly thereafter. Thus, any and all approaches to therapy in this disease have proven to be singularly ineffective up to the present time.

As a sequellae of the delineation of this new disease entity, there will inevitably be a larger number of cases reported in the future. Whether the entity will remain confined to children of Jewish extraction with wider reporting of cases remains to be seen. An awareness of this clinical entity should allow a diagnosis of familial autonomic dysfunction to be made very early in the postnatal period.

REFERENCE

1. Riley, C. M.: Familial Autonomic Dysfunction. J. A. M. A. **149**: 1532 (August), 1952.

CLINICO-PATHOLOGICAL CONFERENCE

Directed by: E. Clarence Rice, M.D.
Assisted by: June Pollack, M.D.
By Invitation: Milton Greenberg, M.D.

June R. Pollack, M.D.

A four year old white girl was admitted to Children's Hospital because of lack of appetite, a low grade fever, and intermittent numbness of the lateral aspect of the left thigh, which had persisted for two weeks. There was no joint or abdominal pain.

The patient was born normally at term. She had had influenza five months before admission and the only other illnesses were occasional colds and sore throats.

The parents and a sixteen months old brother were well. There was no history of familial diseases.

She was well developed but thin and somewhat pale. She had no definite complaints and did not appear acutely ill. Both ear drums were slightly injected and the light reflex was absent on the left. The tonsils were enlarged and the pharynx was mildly inflamed. The heart rate was 120 per minute and since the point of maximum impulse was just lateral to the midclavicular line the heart was thought to be slightly enlarged. There was a questionable apical systolic murmur. During this admission the extremities were subjectively and objectively negative, the reflexes were normal and bilaterally equal. During the 26 hour period of hospitalization the temperature ranged between 99.0° and 100.8°.

The urine was normal with a specific gravity of 1.021. The red blood cell count was 2.95 million with 8.5 grams of hemoglobin. The white blood cell count was 13,000 and the differential was normal. X-ray examination of the lower spine and the proximal third of the femora showed a slight scoliosis with the convexity to the right in the region of the twelfth rib. A flat plate of the abdomen was negative, the psoas muscles being fairly well outlined.

The diagnosis was bilateral otitis media at the time of discharge. Six days later she was limping and was readmitted because of pain in the left leg. The pain in the lateral aspect of the left thigh was aggravated by pressure and was present usually at night. Four days before readmission her neck had become painful and remained so for two days. Anorexia had persisted. Her temperature averaged 100.0° during the day and was between 101.0°–103.0° at night. Sweating cocurred in the afternoon and at night. She tired easily but would play much of the time.

She was very uncooperative, appeared chronically ill and showed moderate pallor. There was slight tonsillar hypertrophy without inflammation. Questionable dullness and decrease in the breath sounds were elicited over the lower lobes bilaterally. The heart was questionably enlarged, the rate was 125 per minute and the sounds were loud, there was a short systolic, grade 1, apical murmur. The liver was palpable but non-tender three centimeters below the left margin. Examination of the extremities revealed the muscle tone to be poor, but there was no definite tenderness. Reflexes were hyperactive but bilaterally equal.

The red blood cell count was 3.45 million with 11 grams of hemoglobin. The white blood cell count was 18,000 and the differential and thrombocyte counts were normal. Urinalyses were consistently normal. The sedimentation rate was 52 millimeters per hour. An agglutination test for Brucella abortus infection was negative.

The blood was cultured three times at intervals of over two weeks. The reports

were respectively: Streptococcus anhemolyticus, Staphyloccocus albus, and Staphylococcus albus hemolyticus. An x-ray examination of the cervical and lumbar spines, the upper portions of the femora and a flat plate of the abdomen were all negative. A chest x-ray indicated a marked increase in fibrosis throughout both lungs suggestive of a bronchitic condition. The heart appeared enlarged to the left and the left border did not present its normal contour.

The fever was remittant in type, being between 99° and 103°. Her appetite was poor. Her left leg continued to be painful mainly in the region of the hip, the pain being aggravated by movement. After three weeks the pain was constant and sometimes was severe enough to make her cry, being localized over the distal portion of the left femur which was tender to touch. Seven transfusions were given as a supportive measure and sulfadiazine was administered until four days before her discharge. No response was noted. She was discharged unimproved after 24 days of hospitalization.

Eleven days later she was admitted for the last time. The course had been gradually downhill with loss of weight, continued fever, irritability, rapid reduction of hemoglobin after transfusions, and tachycardia. The liver now extended to the crest of the ilium and was tender. There was pain in the left hip and right leg below the knee. Small discrete pink spots were noted on the abdomen.

The specific gravity of the urine was 1.026. There were 10 milligrams per 100 milliliters of albumin. Many white blood cells, a few granular casts, a few sulfonanide crystals, and a rare red blood cell were reported. The red blood cell count was 3.85 million with 11 grams of hemoglobin. The white blood cell count was 8,800 with 59 per cent lymphocytes. Two thrombocyte counts were 100,000 and 40,000. Coagulation and bleeding times were normal. The sedimentation rate was 46 millimeters per hour. On admission a blood culture was positive for Staphylococcus albus and when repeated two weeks later there was no growth. The Kahn test was negative. The serum phosphorus was 5.3 milligrams and the serum calcium 11.4 milligrams, the acid phosphatase 4 King-Armstrong units and the alkaline phosphatase 28 units. A tibial marrow puncture revealed the myeloid elements to be present in a normal ratio but the erythroblastic elements appeared to be somewhat reduced. The marrow was thought to be essentially normal. X-ray examinations revealed a destructive process which involved the pelvic bones, the upper thirds and distal portions of the femora, also the upper thirds of the humeri. In the skull there was some disturbance of the architecture of the upper portion of the frontal bones and the upper and anterior portions of the parietal bones. These changes were reported to be suggestive of hemotogenous osteomyelitis. An intravenous pyelogram was interpreted as being essentially normal.

The patient was now in the tenth week of her illness. She had not responded to chemotherapy or blood transfusions and had become greatly emaciated. The liver was large and tender and there were occasional purpuric spots present over the skin. She developed dyspnea very suddenly and expired.

DISCUSSION

Milton Greenberg, M.D.

The case under discussion poses a rather comprehensive differential diagnosis and three etiological factors should be considered in view of the facts set forth. These would include infection, malignant tumor and reticuloendotheliosis. I propose to discuss each one of these possible causes in turn.

One would expect an infection such as osteomyelitis to have an onset which would be more abrupt with throbbing pain and movement of the limbs would be painful. In infants the most common cause of osteomyelitis would probably be a streptococcus infection following a hematogenous spread secondary to an upper respiration infection. In older children, osteomyelitis is usually caused by Staphylococcus aureus, the skin being the most frequent portal of entry. Localized pain and swelling would be present even though the x-ray examinations are negative early in the disease. Osteomyelitis is unlikely to have a hematogenous spread to the skull. This disease must be considered although I do not place it high among the diagnostic possibilities.

From the standpoint of the cause being a malignant tumor, a neuroblastoma would have to be considered in the differential diagnosis. An abdominal tumor is usually present although metastases may develop before primary growth is apparent. Often x-ray examination will reveal small deposits of calcium in the tumor. The mass is usually nodular and extends across the abdomen. Symptoms and findings usually consist of fever and anemia with early metastases to the skull as well as to the spine femur, humerus, lungs and liver. A large percentage of patients will usually die within two months of onset. The distal thirds of the upper and lower extremities are rarely involved. Another neoplasm to be considered is Wilms' tumor. The mass is generally palpable and pyelogram often shows displacement of the kidneys pelvis. In the event of metastasis, the lung is usually involved. Other neoplastic diseases such as lymphosarcoma, lymphoblastoma, and Hodgkin's disease are usually accompanied by generalized lymph node enlargement. Leukemia would also have to be considered in the differential diagnosis and usually is accompanied by vague pains in the extremities, anorexia, weakness, fatigue, bruising tendencies and a septic temperature. The spleen may not be palpable in the acute fulminating form. The presence of thrombocytopenia as well as the characteristic changes in the peripheral blood and bone marrow are diagnostic. Metastases may occur and involve the region of the orbits as well as the distal thirds of the upper and lower extremities. In aleukemic leukemia, the hematological picture may be equivocal for long periods and remain inconclusive until death. I would not regard leukemia as a very strong possibility in this patient because of lack of pathognomonic collateral findings.

The reticuloendothelioses or xanthomatoses include Hand-Schüller-Christian, Neimann-Pick, and Gaucher's diseases and have to be considered in the differential diagnosis in view of the bone changes. However, these entities remain unlikely possibilities in the present case. Letterer-Siwe disease, on the other hand, a known familial disease, with an acute onset and fatal termination, must be considered rather seriously. Wide-

spread reticuloentothelial hyperplasia, enlargement of the spleen, liver and lymph nodes together with hypochromic anemia, bone lesions, and a purpuric rash are frequently encountered. The onset is usually insidious, often following or associated with an upper respiratory infection. Weakness, pallor, fatigue, irritability, and anorexia are common early manifestations. Frequently, a moderate fever may be in evidence. Anemia is constant, may be severe and may respond only temporarily to transfusions. The spleen and liver are usually nontender, firm, and moderately to markedly enlarged. Mild to severe thrombocytopenia may be present. X-rays of the bones reveal cystic areas most frequently observed in the flat bones of the skull and pelvis as well as the ribs and long bones. X-rays of the lungs frequently show diffuse parenchymatous infiltration of a non-specific character and dyspnea may be a concomitant symptom.

In the case under discussion, the history of acute illness of ten weeks' duration with enlargement of the liver, hypochromic anemia which was refractory to transfusions, multiple bone lesions of the extremities and skull, a purpuric rash preceded by a small nodular eruption on the abdomen, thrombocytopenia, weakness, pallor, fatigue, anorexia, and septic temperature are consistent with either Letterer-Siwe disease or neuroblastoma. In the absence of an abdominal mass and a negative intravenous pyelogram with no displacement of the kidney, I would favor Letterer-Siwe disease even though no splenic enlargement was described. Neuroblastoma would be my second choice.

PATHOLOGIC DISCUSSION

Dr. June Pollack: The students' diagnoses are as follows: six are in favor of tuberculosis (miliary or tuberculosis of the bone), four believe it to be a osteomyelitis, while three vote for a malignancy.

Dr. Joseph LoPresti: In my opinion the absence of splenomegaly and the older age of this child speak against Letterer-Siwe disease. Usually those with Letterer-Siwe disease are two years of age or younger.

Dr. Milton Greenberg: My experience with Letterer-Siwe disease is limited to only one case, but there have been reports in the literature in which there was no associated splenomegaly and in which children up to about five years of age have had the disease.

Student: Could this be miliary tuberculosis with bone involvement?

Dr. Milton Greenberg: If this were tuberculosis, with this much involvement of the bone, one would expect more extensive pulmonary changes. Usually one does not see as much bone involvement in tuberculosis.

Dr. David F. Bell, Jr.: Usually one does not see much marked bone changes in Letterer-Siwe disease either.

Dr. Milton Greenberg: That is true. Many authors have tried to associate

Letterer-Siwe disease with a bacteremia and have stated that the bone changes resemble those of hematogeneous osteomyelitis in that usually one or several bones are involved rather than the generalized involvement seen in this patient.

Dr. Joseph LoPresti: Why do you not favor the diagnosis of neuroblastoma?

Dr. Milton Greenberg: The skin lesions seen in this case could well be the metastatic skin lesions seen in Letterer-Siwe disease. One may see a low platelet count in both Letterer-Siwe disease and neuroblastoma. This patient's anemia did not respond to transfusions as in the case with the anemia associated with Letterer-Siwe disease.

Dr. Joseph LoPresti: The bone lesions of Letterer-Siwe's disease are usually cystic in type.

Dr. June Pollack: The positive autopsy findings are as follows. The girl was a well developed, emaciated white female of four years of age. There was some protrusion of the right orbit, with ecchymosis and a bluish discoloration of the right side of the face. Bloody fluid was present in the mouth and nose. There were a number of petechial spots varying in size from pin point to pinhead over the thorax and abdomen, and a decubitus ulcer was present on the sacrum.

On reflection of the scalp a number of hemorrhagic areas about 3 to 4 centimeters in size were found. They were soft and located over the upper portions of the frontal and parietal bones. When sectioned, these areas showed proliferation of the bone with the formation of spicules which projected themselves into the adjacent dura which was involved by the metastatic tumor growth. The tissues were quite hemorrhagic in these areas. The bone in the right post-orbital region was involved in a metastatic new growth which was represented by a soft brownish semi-fluid mass of tissue.

Approximately 100 milliliters of bloody fluid was present in both pleural cavities and 150 milliliters of slightly brownish nearly clear fluid was found in the peritoneal cavity. The heart and lungs showed no abnormalities. The liver edge extended 12 centimeters below the right midcostal margin and the surface was somewhat irregular due to numerous grayish tumor masses. These gave a mosaic-like appearance due to the hemorrhagic and cystic areas scattered over the surface. Section revealed light brownish-yellow tissue and small tumor masses varying in size from 0.1 centimeter to 0.5 centimeter and cystic areas filled with hemorrhagic fluid. The adrenals were intact, and the left adrenal was lying on a tumor mass but was not involved in the neoplasm. Just above the left kidney there was a soft regular mass measuring 9 x 5 x 6 centimeters which was adjacent to the left kidney but did not involve it. The tumor extended up as far as the pancreas, around to the kidney and across the vertebra a short distance to the right side of the abdomen.

It lay on the aorta but did not involve it. The sectioned tissue was soft and creamy with some areas of hemorrhage. The adjacent retroperitoneal lymph nodes showed similar involvement. The kidneys showed good differentiation between the cortex and medulla with some evidence of edema. The pelvis of the left kidney was dilated but no evidence of tumor invasion was seen. The ribs and long bones showed periosteal hemorrhages and section revealed metastatic invasion by neoplastic tissue.

Microscopic examination demonstrated the tumor to be composed of densely packed round cells with deeply staining nuclei. There were numerous congested blood vessels scattered throughout and a minimal amount of fibrous connective tissue. No giant cells or mitotic figures were seen. Some of the cells were arranged in groups.

The liver tissue was infiltered by small staining round cells, many arranged in groups, and showing rosette formation similar to that seen in neuroblastoma. Some central areas of hemorrhage were noted.

Sections of the frontal bone, ribs, and long bones showed normal bone and marrow structure with occasional areas of scattered densely packed round cells with deeply staining nuclei.

The retroperitoneal lymph nodes were completely replaced by metastatic tumors.

The final pathologic diagnoses were:

1. Neuroblastoma arising from the abdominal sympathetic nervous system with metastases to retroperitoneal and thoracic lymph nodes, liver, meninges, skull, long bones, and right post-orbital region.
2. Purpura involving skin, epicardium and bladder mucosa.
3. Pleural effusion, bilateral.
4. Pulmonary congestion, edema and atelectasis.
5. Abdominal ascites.
6. Fatty metamorphosis of the liver.
7. Hydronephrosis and hydroureter, left.
8. Decubitus ulcer, sacrum.

Dr. Milton Greenberg: This case illustrates the importance of a good physical examination. It would have been of great importance to have determined if the liver was smooth or nodular and this was not stated in the protocol. Also, I believe the intravenous pyelogram was abnormal and showed dilatation of the pelvis of the left kidney.

Dr. E. Clarence Rice: Wilms' tumor and neuroblastoma are the two most frequent tumors in childhood. When one feels an abdominal mass it calls for prompt follow-up with intravenous pyelograms. Neuroblastoma frequently metastasizes to the bones of the orbit and whenever one has an abdominal mass and proptosis, he should think of neuroblastoma. Today one can take a more optimistic view of the treatment of neuroblastomas.

First, if they are recognized and removed promptly, and receive post-operative X-ray therapy, one may possibly effect a cure. They are radio-sensitive. Secondly, these tumors behave strangely, in that instances are known of a child having a laparotomy and a biopsy of a tumor taken and the incision closed. The diagnosis of neuroblastoma is made but the child continues to live for years with apparent disappearance of the tumor. Then too, we have chemotherapuetic agents which can be therapeutically active. Even in patients with metastases, there are instances where the tumor was removed, post-operative X-ray treatment given with survival of the child.

Dr. David F. Bell, Jr.: The ratio of Wilms' tumor to neuroblastoma in this hosital is 2:1.